Drugs for glaucoma

Ivan Goldberg, Eye Associates and Glaucoma Service, Sydney Eye Hospital and the Save Sight Institute, University of Sydney, Sydney

SYNOPSIS

Older drugs for glaucoma reduce intra-ocular pressure, but often have unpleasant adverse effects. They still have a role in therapy, but there are now newer drugs which overcome some of the problems. The topical carbonic anhydrase inhibitors decrease the secretion of aqueous humour, while lipid-receptor agonists increase uveoscleral outflow. Alpha$_2$ agonists use both mechanisms to reduce intra-ocular pressure. If a patient needs more than one drug to control their glaucoma, the new drugs generally have an additive effect when used in combination regimens.

Index words: beta blockers, carbonic anhydrase inhibitors, lipid-receptor agonists.

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Introduction

Glaucoma is the second commonest cause of visual disability in the world.[1] It affects between 70 and 90 million people, with about 10% of them becoming blind in both eyes.[2]

In the last decade there has been an increase in the number of drugs available to treat glaucoma. However the key strategy remains the reduction of intra-ocular pressure. Many of the older drugs remain available so we need to assess how the new drugs fit in with them and which drugs should be replaced.

The old staples

Beta blockers, adrenergics, miotics and systemic carbonic anhydrase inhibitors were the four families of antiglaucoma drugs. Most are still available (Tables 1 and 2).

Beta blockers

Beta blockers remain the most commonly prescribed antiglaucoma drugs, but their usage is falling relative to the newer preparations. Timolol can be instilled once or twice daily with equal effect for most patients. Betaxolol is needed twice daily and its ocular hypotensive efficacy is not as marked. While betaxolol possesses calcium channel blocking properties, which offer anti-vasospastic and anti-apoptotic potential, these effects have not been proven clinically to reduce glaucomatous visual loss.

With remarkably few topical adverse effects (surface irritation or conjunctival hyperaemia in a small number of patients), timolol and levobunolol inhibit the rate of aqueous production by about 40%. This drops the intra-ocular pressure by 20–25%, which is more than the 15–20% drop with betaxolol. With longer-term use of timolol or levobunolol, tachyphylaxis is not uncommon and the pressure slowly rises. Withdrawing the drug for a few months often re-establishes its efficacy.

The main problem with timolol or levobunolol is their potential for systemic adverse effects. These are the same as the adverse effects of oral beta blockers, the most important of which are bronchoconstriction, bradyarrhythmias, and an increase in falls in the elderly.

As betaxolol is relatively selective for beta$_1$ receptors it should pose less respiratory risk. Its pharmacokinetic properties (higher plasma binding and larger volume of distribution) also make it less likely to provoke other systemic effects.

Miotics

Miotics (pilocarpine and carbachol) are rapidly falling out of favour. While their ocular hypotensive efficacy is undisputed, and their systemic safety margin wide (abdominal cramping or diarrhoea are rarely reported), their use is declining because of their local effects and the need to instill them up to four times daily. As parasympathomimetics, these drugs lower intra-ocular pressure by stimulating the ciliary muscle to exert a physical tug on the trabecular meshwork. This stimulation also causes browache and accommodative spasm (the fluctuating myopia is very distracting particularly for younger patients). Constriction of the sphincter pupillae produces miosis, which dims vision especially in older patients with cataracts. The miosis is uncosmetic, and creates technical problems from poor mydriasis if cataract extraction surgery is needed after years of instillation.

Adrenergic agonists

Dipivefrine is the only non-selective adrenergic agonist still available. Relatively low hypotensive efficacy, not infrequent surface irritation and frank allergic blepharoconjunctivitis have translated its unattractiveness (even when nothing better was available) into unpopularity. Safer than the now unavailable adrenaline products, it is still prescribed occasionally, and, like beta blockers and miotics, is additive in its effect with all the other older drugs.

Systemic carbonic anhydrase inhibitors

Acetazolamide is the only remaining systemic carbonic anhydrase inhibitor in Australia. It is still the most potent ocular hypotensive medication available, and can drop intra-ocular pressure by 25–40%. Other than rare transient myopia, no ocular adverse effects occur. Systemic adverse effects are legion – anorexia, nausea, abdominal cramping, diarrhoea, anergy, weight loss and paraesthesiae. As acetazolamide is related to sulfonamides, allergic reactions (including Stevens-Johnson syndrome) and aplastic anaemia have been a concern.[3]

Table 1

Clinically important pharmacological properties of antiglaucoma medications

	Concentration	*Instillation frequency*	*Duration of effect*
Inhibit aqueous inflow			
Beta blockers			
$\underline{\text{Beta}_1}$			
Betaxolol	solution 0.5% suspension 0.25%	2/day	12–18 hours
$\underline{\text{Beta}_1 \text{ and beta}_2}$			
Timolol	solution 0.25%, 0.5% gel 0.25%, 0.5%	1–2/day	12–24 hours
Levobunolol	solution 0.25%	1–2/day	12–24 hours
Systemic carbonic anhydrase inhibitors			
Acetazolamide	250 mg tablets	½–4 tablets/day	6–12 hours
Topical carbonic anhydrase inhibitors			
Dorzolamide	solution 2%	2–3/day	8–12 hours
Brinzolamide	suspension 1%	2–3/day	8–12 hours
Enhance conventional aqueous outflow (via trabecular meshwork)			
Miotics – direct parasympathomimetics			
Pilocarpine	solution 0.5%, 1%, 2%, 3%, 4%, 6%	2–4/day	4–12 hours
Carbachol	solution 1.5%, 3%	2–4/day	4–12 hours
Adrenergic drugs – may increase uveoscleral aqueous outflow as well			
Dipivefrine	solution 0.1%	2/day	12–18 hours
Enhance uveoscleral (unconventional) outflow			
Lipid-receptor agonists			
Latanoprost	0.005%	once daily	24–36 hours
Travoprost	0.004%	once daily	24–36 hours
Bimatoprost	0.03%	once daily	24–36 hours
Unoprostone	0.15%	2/day	12–18 hours
Dual action (aqueous inflow inhibition and uveoscleral outflow enhancement)			
Alpha_2 agonists			
Brimonidine	0.2%	2–3/day	8–12 hours
Fixed combinations			
Timolol/dorzolamide	0.5% / 2%	2/day	12 hours
Timolol/latanoprost	0.5% / 0.005%	once daily	24 hours

Table 2

Possible additive effects between different classes of antiglaucoma drugs

	Beta blockers	*Adrenergics*	*Miotics*	*Systemic CAIs**	*Topical CAIs**	*Alpha_2 agonists*	*Lipid-receptor agonists*
Beta blockers	–	+	+++	+++	+++	+++	+++
Adrenergics	+	–	+++	+++	+++	–	–
Miotics	+++	+++	–	+++	+++	+++	++
Systemic CAIs*	+++	+++	+++	–	–	+++	+++
Topical CAIs*	+++	+++	+++	–	–	+++	+++
Alpha_2 agonists	+++	–	+++	+++	+++	–	+++
Lipid-receptor agonists	+++	–	++	+++	+++	+++	–

* CAIs carbonic anhydrase inhibitors
– Not recommended
\+ Partially additive
++ May be additive, but not invariably
+++ Fully additive

Renal calculi are not uncommon. When necessary, acetazolamide should be used for as short a term as possible.

The new drugs

While the ultimate goal of a universally effective, totally safe and perfectly tolerable drug has not been realised, the newer drugs represent a series of distinct advances (Table 1).

Lipid-receptor agonists and related drugs

Latanoprost was the first of this class to be generally available, and it climbed rapidly to the position of most frequently prescribed drug for glaucoma, despite complaints about its cost. For the majority of patients, one drop of latanoprost 0.005% once daily will lower intra-ocular pressure by 27–34%.[4] This allows it to replace multidrug therapy in many patients.[5] This has an immediate flow-on benefit in terms of compliance, convenience and overall cost. No significant loss in the reduction in intra-ocular pressure has been found after 24 months of treatment.[6] With their long duration of action, latanoprost and similar drugs ensure better control of intra-ocular pressure throughout the day and night.

Latanoprost increases the flow of aqueous fluid through the ciliary muscle and through the sclera into the orbit, thereby enhancing uveoscleral or 'unconventional' outflow. Probably because of its unique mechanism of action, latanoprost is additive with all other antiglaucoma drugs with the possible exception of miotics, particularly in patients who have been using high concentrations of miotics for years.

Travoprost is available in Australia. There is also bimatoprost, whose manufacturer cites evidence that it activates a different class of lipid receptors and belongs to a different class of drugs (prostamides).

Slight conjunctival hyperaemia and a new adverse effect, increased iris pigmentation, were the main adverse events in all clinical trials of lipid-receptor agonists. Patients with hazel or mixed colour irides seem most predisposed; the iris colour changes are irreversible, but not progressive once the drug has been withdrawn.[7] These effects have also been reported with unoprostone, travoprost and bimatoprost. Darker, thicker and longer eyelid lashes ('luscious lashes' – quite popular with some patients) are almost invariable, and are reversible once the drug has been discontinued.[8] These local effects may be more common with travoprost and bimatoprost than with latanoprost. The ocular hypotensive effect of these two is at least as good as that of latanoprost as currently constituted, and may be slightly better.

Other less common adverse effects, which have emerged following marketing, include anterior uveitis and cystoid macular oedema. Confined mainly to patients with already predisposed pseudophakic or aphakic vitrectomised eyes, these problems are unusual, and usually diminish with drug withdrawal. As adverse effects may only emerge some time after marketing any new drug, clinicians need to consider whether any symptoms or problems experienced by patients using such a drug are causally related to that drug.

Alpha$_2$ agonists

Based on clonidine, apraclonidine and brimonidine are the two topical alpha$_2$ selective agonists available in Australia. Stimulation of alpha$_2$ receptors lowers intra-ocular pressure, whereas alpha$_1$ receptor activation produces adverse effects such as mydriasis, eyelid retraction and vasoconstriction.

Apraclonidine is 30 times less selective than brimonidine for the alpha$_2$ receptor. As it also often causes tachyphylaxis and allergic blepharoconjunctivitis, apraclonidine is not recommended for chronic control of glaucoma. Apraclonidine remains very useful in controlling an attack of angle-closure glaucoma and in preventing possible spikes of intra-ocular pressure after anterior segment laser surgery.[9]

Brimonidine reduces intra-ocular pressure by inhibiting aqueous production and increasing uveoscleral outflow. The former mechanism is thought to be more important early in treatment while the latter is more significant during prolonged treatment. The mean peak effect of brimonidine is a 24% reduction in intra-ocular pressure and the mean trough effect is a 15% reduction.[10] Little if any tachyphylaxis has been reported after two years of treatment. After four years of instillation by patients who have responded to brimonidine, the trough effect increases to approximate the peak.

Common adverse events of alpha$_2$ agonists include conjunctival hyperaemia (11%), allergic blepharoconjunctivitis (cumulative over four years to 25%), foreign body sensation and stinging. Dry mouth, headache, fatigue and drowsiness may be experienced, particularly if the patient is instilling the drops without adequate no-blinking/nasolacrimal duct occlusion techniques (see Fig. 1).

Monoamine oxidase inhibitors are a contraindication to the use of brimonidine. It should be used with caution in patients taking tricyclic antidepressants, barbiturates, sedatives, beta blockers, calcium channel blockers or other systemic antihypertensive drugs.

While the adverse effect profile of brimonidine is generally favourable, it depends critically on an intact blood-brain barrier. In infants and younger children this is not the case and topical brimonidine can cause profound systemic hypotension, apnoea, convulsions and cyanosis. It is absolutely contraindicated in children under the age of six, and relatively contraindicated in older children.

Topical carbonic anhydrase inhibitors

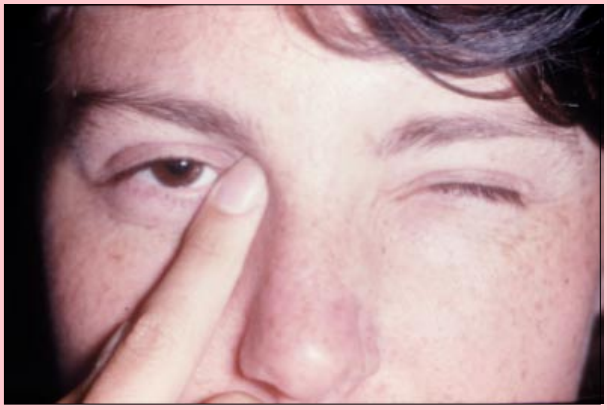
The topical carbonic anhydrase inhibitors, dorzolamide and brinzolamide, reduce intra-ocular pressure by 15–24% with less apparent systemic effects than acetazolamide, and reasonable surface comfort.[11] Both drugs seem to have very similar pharmacological and clinical profiles. They need twice or even three times daily instillations and are only occasionally satisfactory as monotherapy. Mostly they are useful as adjunctive drugs – when added to timolol, for example, a further 15–20% reduction in intra-ocular pressure can be anticipated.[12] They are not as effective as systemic carbonic

Fig. 1

Duct occlusion techniques

Simple eyelid closure AND digital occlusion of the tear duct for at least two minutes after eye drop instillation reduces systemic absorption of any topical drug by up to two-thirds. Thereby, the safety margin of any instilled medication can be expanded significantly.

(The photo shows the two techniques separately. Ideally the patient uses both techniques on the same eye.)



anhydrase inhibitors and they should not be prescribed simultaneously with acetazolamide.[13]

Corneal disease, particularly the stromal oedema effects of endothelial dysfunction, can be aggravated by topical carbonic anhydrase inhibitors. In healthy eyes, this does not seem to be a problem. The most common ocular adverse events with dorzolamide are stinging (less with brinzolamide), burning and eyelid inflammation. Allergic conjunctivitis leads to about one patient in 20 discontinuing treatment over 12 months. Conjunctival hyperaemia and follicles occur in up to 20% of users. Continued use seems to be associated with a declining rate of problems.

Following drainage surgery and treatment with systemic carbonic anhydrase inhibitors, hypotony and cilio-choroidal detachment have been reported. These adverse effects appear to be less frequent with dorzolamide.

Fixed combinations

To improve convenience and thus compliance, there is a trend to introduce fixed combinations of old and new drugs. While the combination of timolol with pilocarpine has been with us for many years, the combination of timolol and dorzolamide has recently been introduced. There will soon be a combination of latanoprost with timolol. Combinations of brimonidine and timolol, as well as travoprost and timolol are also on their way.

New choices – new responsibilities

All that we do in our management of patients depends on the balance between possible benefits versus potential harm. For the vast majority of our patients, medical therapy of glaucoma remains the first and ongoing strategy. Being asymptomatic, chronic and incurable (but generally controllable) diseases, the glaucomas by their very nature encourage non-compliance. It is the treatment which produces adverse effects, engenders inconvenience and costs, and diminishes quality of life. Instructing the patient in techniques to reduce the rate of systemic absorption of any topical ophthalmic drug, significantly widens its safety margin. Ideally all patients instilling eye drops of any sort should be shown how to perform this simple manoeuvre (see Fig. 1).

The number of new drugs which reduce intra-ocular pressure improves efficacy and safety margins, but even more importantly, allows us a greater choice for each individual patient. To exercise that choice meaningfully, we need the evidence of likely strengths and weaknesses of each of these medications, and how they interact with one another (Table 2) and with other drugs being used for concomitant disease.

Since latanoprost was introduced, it has steadily displaced the non-selective beta blockers as first-line therapy. The availability now of travoprost, and soon of bimatoprost, extends the number of patients who have a good chance of responding well to one of these drugs. Their once-daily instillation and wide safety margin should improve compliance. Brimonidine is usually a second-line drug, but may be used instead of beta blockers as first choice, particularly in the presence of pulmonary and/or cardiovascular disease. Topical carbonic anhydrase inhibitors are often introduced as third-line drugs. All can be used adjunctively.

E-mail: igoldber@bigpond.net.au

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FURTHER READING

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 151)

7. Alpha$_2$ agonists cause a greater reduction in intra-ocular pressure than lipid-receptor agonists.
8. Latanoprost should not be used in combination with a topical beta blocker in the treatment of glaucoma.

Patient support organisation

Glaucoma Australia

Glaucoma Australia aims to minimise sight disability from glaucoma by:

- increasing community awareness and understanding of glaucoma and the need for regular eye checks
- supporting glaucoma patients and their families particularly with information
- funding glaucoma research.

Glaucoma Australia disseminates a newsletter and information about new developments in glaucoma medicines, diagnostic equipment and therapeutic procedures. Glaucoma Australia Support Groups in most States provide, through guest speakers, education and information on glaucoma, and members offer mutual support to glaucoma sufferers, their families and friends.

Contacts

Glaucoma Australia Inc.
1st Floor AMA House
33-35 Aitchison Street
St Leonards NSW 2065
PO Box 420
Crows Nest NSW 1585
Web site: www.glaucoma.org.au
Phone: (02) 9906 6640, Freecall 1800 500 880
E-mail: glaucoma@glaucoma.org.au

For details on glaucoma meetings in South Australia, Tasmania and Victoria contact the Glaucoma Australia Melbourne office, phone (03) 9404 2974.

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Contacts

Australian Medicines Handbook Pty Ltd
PO Box 240 Rundle Mall
Adelaide SA 5000
Phone: (08) 8303 6977
Fax: (08) 8303 6980
E-mail: amh@amh.net.au
Web site: www.amh.net.au